UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT **DIETHANOLAMINE SALT OF 2,4-D ACID:** Acute Toxicity Studies and a 21-day Dermal Toxicity Study.

FROM: Jess Rowland, M.S, Toxicologist Jess Rowland 2/19/92
Section II, Toxicology Branch II
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TO: W.Waldrop / J.Coombs
Product Manager (71)
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THRU: K.Clark Swentzel, Section Head K. Clark Swentzel 2/19/92
Section II, Toxicology Branch II
Health Effects Division (H7509C)
and
Marcia van Gemert, Ph.D., Chief J M Joanne for 2-20-92
Toxicology Branch II
Health Effects Division (H7509C)

PROJECT/STUDY IDENTIFICATIONS: Submission: S401514

HED Project No. 1-2160 Caswell No. 315 K

TRID No(s): 419209-01; 429209-02; 419209-03; 419209-04; 419209-05; 419209-11; and 419866-01

Registrant: PBI / Gordon Corporation., Kansas City, MO

ACTION REQUESTED: In-depth review of acute toxicity studies, and a 21-day dermal toxicity study with the Diethanolamine salt of 2,4-Dichlorophenoxyacetic Acid [2,4-D DEA].

RESPONSE: The acute toxicity, [oral, dermal, inhalation, eye and skin irritation, and dermal sensitization studies], and a 21-day dermal toxicity study of **Diethanolamine salt of 2,4-dichlorophenoxyacetic acid, are classified as CORE GUIDELINE and ratisfy Guideline requirements 81-1, 81-2, 81-3, 81-4, 81-5, 81-6, and 82-2, respectively.** A seperate Data Evaluation Report for each of study is attached. The results of each study is as tabulated below:

STUDY	MRID No.	RESULTS	TOX.CATEGORY	CORE CLASSIFICATION
81-1 Acute oral LD50 Species: Rat Ricerca; 90-0161 07/13/90	419209-01	LD_{50}= 1170 mg/kg for males 735 mg/kg for females 910 for combined sexes	III	Guideline
81-2 Acute dermal LD50 Species: Rabbit Ricerca; 90-0162 06/27/90	419209-11	LD_{50}=>2000 mg/kg	III	Guideline
81-3 Acute inhalation LD50 Species: Rat Huntington;90-0163 10/20/90	419866-01	No compound-related toxicity at the maximum attainable concentration of 3.5 mg/L during a 4 hour exposure. The nominal concentration was 28.2 mg/L LC_{50}=> 3.5 mg/L	III	Guideline
81-4 Primary Eye Irritation Species: Rabbit Ricerca; 90-0164 07/13/90	419209-02	Severe eye irritant. PIS = 71.3/110	I	Guideline
81-5 Primary Dermal Irritation Species: Rabbit Ricerca; 90-0165 06/27/90	419209-03	Slight skin irritant. PIS = 1.6/8	IV	Guideline
81-6 Dermal Sensitization Species: Guinea pig Ricerca; 90-0166 07/13/90	419209-04	Non sensitizer	NA	Guideline
82-2 21-Day Dermal Toxicity Species: Rabbit Springborn; 3229.1 02/04/91	419209-5	Dose levels tested: 0, 15, 148, 443 mg/kg/day, 6 hr/day for 21 days. No treatment-related effects on survival, body weight, body weight gain, hematology, urinalyses, or gross pathology. Dermal irritation was dose-dependent; however, no microscopic skin lesions at 15 mg/kg/day. Histopathological lesions at 148 and 443 mg/kg/day. No systemic toxicity at 15 or 148 mg/kg/day. Systemic toxicity at 443 mg/kg/day included increased enzyme levels [AST, ALT,Alk.Phospl, increase in liver weights, and liver lesions. Dermal Toxicity NOEL = 15 mg/kg/day LOEL = 148 mg/kg/day Systemic Toxicity NOEL = 148 mg/kg/day LOEL = 443 mg/kg/day		Guideline

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PRIMARY REVIEWER: Jess Rowland, M.S, Toxicologist Jess Rowland 2/19/92
Section II, Toxicology Branch II

SECONDARY REVIEWER: K. Clark Swentzel, Section Head K. Clark Swentzel 2/21/92
Section II, Toxicology Branch II

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity **GUIDELINE:** 81-1

Caswell No. 315 K **MRID No. 419209-01** **HED PROJECT No. 1-2160**

TEST MATERIAL: Diethanolamine salt of 2,4-D.

REGISTRANT: PBI/Gordon Corporation, Kansas City, MO

TESTING LABORATORY: Ricerca, Inc. Department of Toxicology and Metabolism. Painesville, OH.

STUDY IDENTIFICATION: 90-0161

TITLE OF REPORT: Acute Oral Toxicity [LD_{50}] Study in Rats with Diethanolamine Salt of 2,4-D.

DOCUMENT NUMBER: 3592-90-0161-TX-001

AUTHORS: S.K. Shults, A.W. Brock, and J.C. Killeen.

STUDY COMPLETION DATE: July 13, 1990

CONCLUSION: The acute oral toxicity of the Diethanolamine salt of 2,4-D (73.09%) was evaluated in male and female Sprague-Dawley rats. The LD_{50} values were 1170 mg/kg for males, 735 mg/kg for females, and 910 mg/kg for the combined sex with 95% confidence limits of 730 to 1160 mg/kg.

TOXICITY CATEGORY: III

CORE CLASSIFICATION: **Guideline;** satisfies Guideline requirement [81-1] for an acute oral toxicity study.

I. INTRODUCTION

This Data Evaluation Report (DER) summarizes the experimental procedures and results of an acute oral toxicity study of 2,4-D DEA in rats.

II. MATERIALS AND METHODS

1. Test Material

Chemical Name:	Diethanolamine Salt of 2,4-D
Active Ingredient:	73.09%
Batch/Lot No.	0017
Description:	Amber liquid

2. Test Animals

Species:	Rats
Strain:	Sprague-Dawley, ZML:SD [SPF]
Sex:	Males and Females
Weight:	M-230-269 g; F-230-271 g
Identification:	Ear tags.

3. Animal Husbandry

Housing:	1/cage.
Food:	Purina Certified Rodent Chow #5002 ad libitum
Water:	tap water ad libitum
Environment:	Temperature- 67 - 75° F; Humidity- 40-70% 12-hour light/dark cycle; 9 air changes/hr.

4. Treatment

Following an overnight fast, groups of five male and five female rats were given a single oral administration of 2,4-D DEA at 500, 700, 1000, or 1400 mg/kg in deionized water [10 ml/kg]. The test material/vehicle mixture were stirred on a stir plate prior to and during dosing of animals. Animals were observed for clinical signs of toxicity at approximately 1, 2.5, and 4 hours post-treatment and daily during the 14-day period. Body weights were obtained prior to treatment, on the day of treatment and on days 7 and 14. Following a 14-day observation period, all animals were sacrificed and a complete necropsy was performed.

5. Quality Assurance

A quality assurance statement was signed and dated July 12, 1991.

III. RESULTS

1. Mortality

Dose (mg/kg)	Male	Female
500	0/5	0/5
700	1/5	3/5
1000	2/5	4/5
1400	3/5	5/5

2. Clinical Observations

Clinical signs common in each of the dose groups were dried red material around the nose, mouth and/or forepaws, ataxia, a decrease in activity and a decrease in the amount of feces.

3. Body Weight

Body weight gains were noted in the surviving rats by days 7 and 14 of the study.

4. Necropsy

Slightly enlarged adrenals were seen in two rats at 700 mg/kg that died during the study. A dilated renal pelvis was observed in two rats at 1000 mg/kg. The only finding seen during terminal necropsy was a dilated renal pelvis in one rat at 500 mg/kg.

IV. CONCLUSION

The acute oral toxicity of 2,4-D DEA was evaluated in male and female Sprague-Dawley rats. The LD_{50} values were 1170 mg/kg for males, 735 mg/kg for females, and 910 mg/kg for the combined sex with 95% confidence limits of 730 to 1160 mg/kg.

TOXICITY CATEGORY: III

V. CORE CLASSIFICATION: Guideline; satisfies Guideline requirement [81-1] for an acute oral toxicity study.

PRIMARY REVIEWER: Jess Rowland, M.S, Toxicologist 2/19/92
Section II, Toxicology Branch II

SECONDARY REVIEWER: K. Clark Swentzel, Section Head
Section II, Toxicology Branch II 2/21/92

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity **GUIDELINE:** 81-2

Caswell No. 315 K **MRID No. 419209-11** **HED PROJECT No. 1-2160**

TEST MATERIAL: Diethanolamine salt of 2,4-D

REGISTRANT: PBI/Gordon Corporation, Kansas City, MO

TESTING LABORATORY: Ricerca Inc., Department of Toxicology and Metabolism, Painesville, OH.

STUDY IDENTIFICATION: 90-0162

TITLE OF REPORT: Acute Dermal Toxicity Study in Albino Rabbits with Diethanolamine Salt of 2,4-D.

DOCUMENT NUMBER: 3592-90-0162-TX-2

AUTHORS: S.K. Shultz, A.W. Brock and J.C. Killeen

STUDY COMPLETION DATE: June 27, 1990

CONCLUSION: The acute dermal toxicity of diethanolamine salt of 2,4-dichlorophenoxyacetic acid (73.09%) was evaluated in male and female New Zealand White Rabbits. The dermal LD_{50} value was greater than 2000 mg/kg [Limit dose].

TOXICITY CATEGORY: III

CORE CLASSIFICATION: **Guideline**; satisfies Guideline requirement [81-2] for an acute dermal toxicity study.

I. INTRODUCTION

This Data Evaluation Report (DER) summarizes the experimental procedures and results of an acute dermal toxicity study of 2,4-D DEA in rabbits.

II. MATERIALS AND METHODS

1. Test Material

Chemical Name: Diethanolamine Salt of 2,4-D
Active Ingredient: 73.09%
Batch/Lot No. 0017
Description: Amber liquid

2. Test Animals

Species: Rabbit
Strain: New Zealand White
Sex: Males and Females
Weight: 2.5 to 3.0 kg
Identification: Ear tags.

3. Animal Husbandry

Housing: 1/cage.
Food: Purina Certified Rabbit Chow #5326 ad libitum
Water: Tap water ad libitum
Environment: Temperature - 62 - 70°F; Humidity- 40-70%
12 hr light/dark cycle;11 air changes/hr

4. Treatment

Following the removal of hair from the dorsal and ventral area of the trunk 24 hours earlier, groups of 5 male and 5 female rabbits were treated with a single dermal application of undiluted test material at 2000 mg/kg to cover an area of approximately 10% of the total body surface of each rabbit. Following application of the test material, a 4" x 8" gauze patch, which was backed by hypoallergenic Dermicel tape, was applied to the site and secured in place with the Dermicel tape. To further secure the patch, the trunk of the animal was wrapped with elastic Vetrap which was secured at either end with Dermiform tape. A plastic restraining collar was placed around the rabbit's neck and the animal was returned to the cage. Following a 24-hour exposure period, the cuffs were removed, observations were made for any reaction at the site of application. The skin was gently wiped, using disposable paper towels which were wetted with water, to aid in the removal of any remaining test material. Rabbits were observed for clinical signs of toxicity at approximately 1, 2.5 and 4 hours post-treatment and daily thereafter. Body weights were obtained prior to treatment, and on days 7 and 14 days. Following a 2-week observation period, all animals were sacrificed and a complete necropsy was performed.

5. Quality Assurance

A quality assurance statement was signed dated on June 26, 1990.

III. RESULTS

1. Mortality

Except for one male rabbit that was found dead one day after treatment, no other mortality occurred during the study. No treatment-related changes were seen at necropsy in the animal that was found dead.

2. Dermal Observations

Lesion	Day 1	Day 3	Day 7	Day 10	Day 14
Erythema: Very slight	None	1 F	None	1 M	1 M
Well defined	3 M 4 F	2 M 3 F	1 M 2 F	2 F	1 F
Moderate to severe	1 M 1 F	None	None	None	None
Edema: Very slight	1 M	1 M	None	None	None
Slight	1 F	None	None	None	None
Moderate	1 M 2 F	None	None	None	None

3. Body Weight

Surviving rabbits gained weight during the 14-day period.

4. Necropsy

No gross treatment-related changes were observed in any rabbits at termination.

IV. CONCLUSION

The acute dermal toxicity of diethanolamine salt of 2,4-D (73.09%) was evaluated in male and female New Zealand White Rabbits. The dermal LD_{50} was greater than 2000 mg/kg [limit dose].

TOXICITY CATEGORY: III

V. CORE CLASSIFICATION: Guideline; satisfies Guideline requirement [81-2] for an acute dermal toxicity study.

PRIMARY REVIEWER: Jess Rowland, M.S, Toxicologist
Section II, Toxicology Branch II

SECONDARY REVIEWER: K Clark Swentzel, Section Head
Section II, Toxicology Branch II

2/19/92

2/21/92

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation Toxicity **GUIDELINE: 81-3**

Caswell No. 315 K MRID No. 419866-01 HED PROJECT No. 1-2160

TEST MATERIAL: Diethanolamine salt of 2,4-D

REGISTRANT: PBI/Gordon Corporation, Painesville, OH.

TESTING LABORATORY: Huntington Research Center, England.

STUDY IDENTIFICATIONS: Ricerca Study No. 90-0163
HRC Report No. RIC 15/901290

TITLE OF REPORT: Diethanolamine Salt of 2,4-D Acute Inhalation Toxicity in Rats 4-Hour Exposure.

AUTHORS: G.C. Jackson and C.J. Hardy

STUDY COMPLETION DATE: October 20, 1990

CONCLUSION: The acute inhalation toxicity of diethanolamine salt of 2,4-dichlorophenoxyacetic acid [73.09%] was evaluated in male and female Sprague-Dawley rats. The highest attainable concentration (3.5 mg/L) produced no compound-related toxicity. The nominal concentration was 28 mg/L. The inhalation LC_{50} was > 3.5 mg/L.

TOXICITY CATEGORY: III

CORE CLASSIFICATION: Guideline; satisfies Guideline requirement [81-3] for an acute inhalation toxicity study.

I. INTRODUCTION

This Data Evaluation Report (DER) summarizes the experimental procedures and results of an acute inhalation toxicity study of 2,4-D DEA in rats.

II. MATERIALS AND METHODS

1. Test Material

Chemical Name:	Diethanolamine Salt of 2,4-D
Active Ingredient:	73.09%
Batch/Lot No:	0017
Description:	Amber liquid

2. Test Animals

Species:	Rats
Strain:	CD Sprague-Dawley
Sex:	Males and Females
Weight:	226 - 240 g (M); 211 - 228 (F)
Identification:	Ear tattoos.

3. Animal Husbandry

Housing:	1/cage.
Food:	Biosure LAD 1 ad libitum
Water:	tap water ad libitum
Environment:	Temperature - 19 to 25°C; Humidity - 40-70%

4. Treatment

A group of five male and five female rats were exposed for a single 4-hour duration to a test atmosphere containing 2,4-D DEA in the form of respirable droplets. A second group of five male and five female rats serving as controls received clean air only in a similar exposure system for 4 hours. The test material was supplied to an aerosol generator made of stainless steel or glass from a syringe driven at a constant rate by a syringe pump. The compressed air supply to the generator was dried, filtered and oil-free. The whole-body exposure chamber with an internal volume of approximately 120 liters was divided by wire mesh partitions to provide 10 separate animal compartments. The test atmosphere entered through a port at the base center of the chamber and passed out through small holes in the lower edge of the square section. The air flow rate was recorded at 30-minute intervals during the exposure. The number of air changes per hour was approximately 10. A syringe filled with the test material was fitted to the syringe pump and connected to the generator with PTFE tubing. A flow rate of 0.6 mL/minute was selected for the exposure.

5. Quality Assurance

A quality assurance statement was signed and dated December 10, 1990.

III. RESULTS

1. Chamber Atmosphere Conditions During Exposure

Sample	Time	Amount in air (mg/L)	Temperature (range)	Humidity (range)
2.1	0h: 30m	3.74	23 - 24°C	61 -85%
2.2	1h : 00m	3.05	(Test)	(Test)
2.3	2h : 00m	3.47		
2.4	3h : 00m	3.72	22 - 24°	37 - 61%
2.5	3h : 50m	3.42	(Control)	(Control)

Standard deviation: 0.280; Nominal concentration: 28.2 mg/L

2. Particle Size

The mass median aerodynamic diameter (MMAD) of the aerosol was 3.2 μm, while the geometric standard deviation of the particle size distribution was 2.74. Approximately 12% of the particles were less than 1 μm and 25% were less than 1.6 μm in aerodynamic diameter. Particle size analyses indicated that 63% (mean value) of the test material present in the chamber atmosphere was of respirable size (<3.5 μm aerodynamic diameter).

3. Survival

All rats survived the exposure and appeared to be normal throughout the two-week observation period.

4. Clinical Observations

Clinical signs observed during the observation period included exaggerated respiratory movements, wet and matted fur, clear or brown colored discharges from the eyes, brown staining, and increased respiration rate. The wet and matted fur, the brown staining and increased respiration rate persisted for several days. All males and 3/5 females recovered from the exposure by day 7 and the remaining two females recovered by day 11.

5. Body Weight

Body weight gain of exposed rats were comparable to that of the control rats.

6. Necropsy

Dark areas were seen in the lung of a female rat exposed to the test material; no other gross alterations were seen in exposed rats. One female control had pale areas of the liver.

IV. CONCLUSION

The acute inhalation toxicity of diethanolamine salt of 2,4-dichlorophenoxyacetic acid [73.09%] was evaluated in male and female Sprague-Dawley rats. The highest attainable concentration (3.5 mg/L) produced no compound-related toxicity. The nominal concentration was 28.2 mg/L. The inhalation LC_{50} was > 3.5 mg/L.

TOXICITY CATEGORY: III

V. CORE CLASSIFICATION: Guideline; satisfies Guideline requirement [81-3] for an acute inhalation toxicity study.

PRIMARY REVIEWER: Jess Rowland, M.S, Toxicologist
Section II, Toxicology Branch II
Jess Rowland 2/19/92

SECONDARY REVIEWER: K. Clark Swentzel, Section Head
Section II, Toxicology Branch II
K. Clark Swentzel 2/21/92

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation **GUIDELINE: 81-4**

Caswell No. 315 K MRID No. 419209-02 HED PROJECT No. 1-2160

TEST MATERIAL: Diethanolamine salt of 2,4-D

REGISTRANT: PBI/Gordon Corporation, Kansas City, MO

TESTING LABORATORY: Ricerca, Inc., Department of Toxicology and Metabolism., Painsville, OH.

STUDY IDENTIFICATION: 90-0164

DOCUMENT NUMBER: 3592-90-0164-TX-001

TITLE OF REPORT: Primary Eye Irritation Study in Albino Rabbits With Diethanolamine Salt of 2,4-D.

AUTHORS: S.K. Shults, A.W. Brock, and J.C. Killeen

STUDY COMPLETION DATE: July 13, 1990

CONCLUSION: The eye irritation potential of diethanolamine salt of 2,4-dichlorophenoxyacetic acid [73.09%] was evaluated in male and female New Zealand White rabbits. The test material was shown to be a severe eye irritant inducing irreversible ocular effects in each of the six rabbits. A mean maximum total score of 71.3 [out of a possible 110] was observed on Day 7 of the study.

TOXICITY CATEGORY: I

CORE CLASSIFICATION: Guideline; satisfies Guideline requirement [81-4] for a primary eye irritation study.

I. INTRODUCTION

This Data Evaluation Report (DER) summarizes the experimental procedures and results of a primary eye irritation study of 2,4-D DEA in rabbits.

II. MATERIALS AND METHODS

1. Test Material

Chemical Name:	Diethanolamine Salt of 2,4-D
Active Ingredient:	**73.09%**
Batch/Lot No.	0017
Description:	Amber liquid

2. Test Animals

Species: Rabbits
Strain: New Zealand White
Sex: Males and Females
Weight: 2.1 - 2.8 kg
Identification: Ear tags.

3. Animal Husbandry

Housing: 1/cage.
Food: Purina Rodent Chow HF #5326 ad libitum
Water: Tap water ad libitum
Environment: Temperature - 62 - 70°C; Humidity- 40 - 70%
12 hr. light/dark cycle; 11 air changes/hr.

4. Treatment

A dose of 0.1 mL was instilled into the lower conjunctival sac of the right eye of 3 male and 3 female rabbits. The left eye of all rabbits served as controls. The treated eyes of the six rabbits remained unwashed. Both eyes of all rabbits were examined at 1, 24, 48 and 72 hours post-instillation and again on days 4, 7, 10, 14 and 21 days for ocular irritation and lesions.

5. Quality Assurance

A quality assurance statement was signed and dated on July 12, 1990.

III. RESULTS

2,4-D DEA was shown to be a potent eye irritant by inducing irreversible ocular effects in each of the six rabbits. Corneal effects characterized by opacities and vascularization and iridal and conjunctival effects were observed during the study. Corneal opacity and vascularization, and conjunctival effects persisted in rabbits thorough day 21 of the study.

A film of apparent conjunctival tissue was observed covering the corneal surface of the treated eye in three rabbits on day 14 and persisted in these rabbits through day 21 of the study. In addition, a tissue mass covering the corneal surface was seen in two rabbits on days 14 and 21. The mass was red in color and covered the lower right quarter of the corneal surface in both rabbits on day 14 and in one rabbit on day 21.

The incidence of positive ocular effects are presented below:

	Hour				Day				
Observation	1	24	48	72	4	7	10	14	21
Cornea Opacity	6/6	6/6	5/6	5/6	5/6	6/6	6/6	6/6	4/4[a]
Iris Iritis	2/6	6/6	6/6	6/6	6/6	6/6	5/5[b]	1/2[c]	0/2[c]
Conjunctive									
Redness	5/6	6/6	6/6	6/6	6/6	6/6	6/6	4/6	4/6
Chemosis	6/6	6/6	6/6	6/6	6/6	5/6	5/6	5/6	4/6
Discharge	5/6	6/6	6/6	5/6	4/6	4/6	4/6	4/6	3/6

[a] The cornea of 2 rabbits was not scored due to a mass and/or apparent conjunctival tissue covering the corneal surface.

[b] The iris of 1 rabbit was not scored due to severe corneal opacity.

[c] The iris of 4 rabbits was not scored due to apparent conjunctival tissue covering the corneal surface and/or a mass covering the corneal surface.

The maximum mean total score was 71.3, observed on day 7 post-treatment. The maximum individual total score was 101, seen in one rabbit at 48 and 72 hours, and on days 4 and 7 post-treatment.

IV. CONCLUSION: The eye irritation potential of diethanolamine salt of 2,4-dichlorophenoxyacetic acid [73.09%] was evaluated in male and female New Zealand White rabbits. The test material was shown to be a severe eye irritant with a mean maximum total score of 71.3 [out of a possible 110], observed on Day 7 of the study.

TOXICITY CATEGORY: I

V. CORE CLASSIFICATION: Guideline; satisfies Guideline requirement [81-4] for a primary eye irritation study.

PRIMARY REVIEWER: Jess Rowland, M.S, Toxicologist Jess Rowland 2/19/92
Section II, Toxicology Branch II

SECONDARY REVIEWER: K. Clark Swentzel, Section Head K. Clark Swentzel 2/21/92
Section II, Toxicology Branch II

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation **GUIDELINE:** 81-5

Caswell No. 315 K **MRID No. 419209-03** **HED PROJECT No. 1-2160**

TEST MATERIAL: Diethanolamine salt of 2,4-D

REGISTRANT: PBI/Gordon Corporation, Kansas City, MO.

TESTING LABORATORY: Ricerca Inc., Department of Toxicology and Metabolism, Painsville, OH.

STUDY IDENTIFICATION: 90-0165

DOCUMENT NUMBER: 3592-90-0165-TX-001

TITLE OF REPORT: Primary Dermal Irritation Study in Albino Rabbits With Diethanolamine Salt of 2,4-D.

AUTHORS: S.K. Shults, A.W. Brock, and J.C. Killeen

STUDY COMPLETION DATE: June 27, 1990

CONCLUSION: The dermal irritation potential of diethanolamine salt of 2,4-dichlorophenoxyacetic acid [73.09%] was evaluated in male and female New Zealand White rabbits. The test material was shown to be a mild or slight irritant in the rabbit skin with a Primary Irritation Index score of 1.6/8.0.

TOXICITY CATEGORY: IV

CORE CLASSIFICATION: Guideline; satisfies Guideline requirement [81-5] for a primary dermal irritation study.

I. INTRODUCTION

This Data Evaluation Report (DER) summarizes the experimental procedures and results of a primary dermal irritation study of 2,4-D DEA in rabbits.

II. MATERIALS AND METHODS

1. Test Material

Chemical Name:	Diethanolamine Salt of 2,4-D
Active Ingredient:	**73.09%**
Batch/Lot No.	0017
Description:	Amber liquid

2. Test Animals

Species:	Rabbits
Strain:	New Zealand White
Sex:	Males and Females
Weight:	2.1 - 2.7 kg
Identification:	Ear tags.

3. Animal Husbandry

Housing:	1/cage.
Food:	Purina Rodent Chow HF #5326 ad libitum
Water:	Tap water ad libitum
Environment:	Temperature- 21°C; Humidity- 50%

4. Treatment

A dose of 0.5 mL of undiluted test material was applied to the intact skin of shaved backs of three male and three female rabbits at an approximate one inch square area. A gauze patch which as backed by an approximately two inch square section of hypoallergenic Dermicel tape was applied over the site. To further secure the patch, the trunk of the animal was wrapped with an elastic Vetrap which was secured at either end with Dermiform tape. To avoid ingestion of the test material rabbits were fitted with a plastic collar. Each test site was evaluated and scored for erythema, eschar and edema within 30 to 60 minutes and then at 24, 48 and 72 hours and on days 4 through 13 of study.

5. Quality Assurance

A quality assurance statement was signed and dated June 26, 1990.

III. RESULTS

Erythema:

- Very slight to well defined in each of six rabbits from 30 to 60 minutes through the 24-hour interval.
- Very slight to well defined in 4/6 at 48 through 72 hours, and in 3/6 on day 4.
- Well defined in 2/6 on day 5.
- Very slight to well defined in 2/6 on days 6 through 9.
- Very slight in one rabbit through day 12.
- No erythema was seen in any rabbits after day 12.

Edema:

- Very slight to slight in 2/6 at the 30 to 60 minute interval.
- Very slight in 2/6 through the 24 hour interval.
- No edema was seen in any rabbits after 24 hours.

Primary Irritation Index: 1.6/8.0

IV. CONCLUSION: The dermal irritation potential of diethanolamine salt of 2,4-dichlorophenoxyacetic acid [73.09%] was evaluated in male and female New Zealand White rabbits. The test material was shown to be a mild or slight irritant in the rabbit skin with a Primary Irritation Index score of 1.6/8.0.

TOXICITY CATEGORY: IV

V. CORE CLASSIFICATION: Guideline; satisfies Guideline requirement [81-5] for a primary dermal irritation study.

PRIMARY REVIEWER: Jess Rowland, M.S, Toxicologist 2/19/92
Section II, Toxicology Branch II

SECONDARY REVIEWER: K. Clark Swentzel, Section Head 2/21/92
Section II, Toxicology Branch II

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization **GUIDELINE: 81-6**

Caswell No. 315 K MRID No. 419209-04 HED PROJECT No. 1-2160

TEST MATERIAL: Diethanolamine salt of 2,4-D.

REGISTRANT: PBI/Gordon Corporation, Kansas City, MO

TESTING LABORATORY: Ricerca Inc., Department of Toxicology and Metabolism., Painsville, OH.

STUDY IDENTIFICATION: 90-0166

DOCUMENT NUMBER: 3592-90-0166-TX-001

TITLE OF REPORT: Dermal Sensitization Study (Closed-Patch Repeated Insult) in Guinea Pigs with Diethanolamine Salt of 2,4-D.

AUTHORS: S.K. Shults, A.W. Brock, and J.C. Killeen

STUDY COMPELTION DATE: July 13, 1990

CONCLUSION: The dermal sensitization potential of diethanolamine salt of 2,4-dichlorophenoxyacetic acid (73.09%) was evaluated in male and female Hartley guinea pigs. The test material was not considered to be a dermal sensitizer.

CORE CLASSIFICATION: Guideline; satisfies Guideline requirement [81-6] for a dermal sensitization study.

I. INTRODUCTION

This Data Evaluation Report (DER) summarizes the experimental procedures and results of a dermal sensitization study of 2,4-D DEA in guinea pigs.

II. MATERIALS AND METHODS

1. Test Material

Chemical Name:	Diethanolamine Salt of 2,4-D
Active Ingredient:	73.09%
Batch/Lot No.	0017
Description:	Amber liquid

2. Positive and Negative Controls

Positive Control: 1-chloro-2,4-dinitrobenzene
Lot Number: 44F-0565
Physical description: Yellow solid
Vehicles: 80% Ethanol and acetone for preparation of dosing solutions with the positive control

3. Test Animals

Species: Guinea pigs
Strain: Hartley
Sex: Male and female
Weight: 339 - 45 g (M); 325 - 409 (F)
Identification: Ear tags.

4. Animal Husbandry

Housing: 1/cage.
Food: Purina Certified Guinea Pig Chow #5025 ad libitum
Water: Tap water ad libitum
Environment: Temperature-67-75°C; Humidity- 40-70%
12 hours light/dark cycle; 11 air changes/hr.

5. Treatment (Buehler; "Delayed Contact Hypersensitivity in the Guinea Pig," Arch. Dermatol.91: 171-175, 1965)

Group	Test/Control Material	No. of Animals	Concentration	
			Induction	Challenge
1	Test Material	10 M, 10 F	100%	100%
2	DNCB (Positive control)	5 M, 5 F	0.2%	0.06%
3	Test Material (Irritation Control-Challenge)	5 M, 5 F	None	100%
	DNCB (Irritation Control-Challenge)		None	0.06%

Induction Phase: Administrations to a site on the upper right side of the midline of the back, as close to the midline as possible, were repeated once a week for three consecutive weeks, for a total of three applications per animal. The same site on each animal was used for the three induction applications of the test material. The sites for the positive control were changed during the third induction application, as needed, to avoid reapplication of material to skin showing qualitative changes.

Challenge Phase: The single challenge was conducted 13 days after the last induction exposure. At challenge, the test material was applied to animals in Groups 1 and 3 at 100%, and DNCB was applied to pigs in Groups 2 and 3 at 0.06%. The irritation control animals (Group 3) treated at the time of challenge were utilized to differentiate dermal reactions produced by irritation in the test and positive control groups from those produced by sensitization.

For Groups 2 and 3, the materials were administered in the same manner as during the induction phase, but at a site on the opposite side of the midline of the back from the site(s) used for induction. Group 3 animals were subjected to the same procedures as the animals receiving challenge exposures. At this time, applications of the two materials (test and positive control) were made on opposite sides of the midline of the back on each control animal.

6. Observations

Dermal evaluations were made at approximately 24 and 48 hours after exposure during both the induction and challenge phases. Approximately three hours prior to the 24-hour scoring, a depilatory was used to remove the hair at the application site.

Guinea pigs were observed twice daily for mortality and moribundity, once weekly for clinical signs, and body weights were recorded within 30 hours prior to initiation and at termination.

7. Quality Assurance

A quality assurance statement was signed and dated July 12, 1990.

III. RESULTS

The positive control (DNCB) produced slight to moderate erythema and edema in the positive control groups guinea pigs demonstrating the susceptibility of the test animals. However, none of the 20 guinea pigs treated with the undiluted 2,4- D DEA exhibited signs of any dermal reactions.

IV. CONCLUSION: The dermal sensitization potential of diethanolamine salt of 2,4-dichlorophenoxyacetic acid (73.09%) was evaluated in male and female Hartley guinea pigs. The test material was not considered to be a dermal sensitizer.

V. CORE CLASSIFICATION: Guideline; satisfies Guideline requirement [81-6] for a dermal sensitization study.

PRIMARY REVIEWER: Jess Rowland, M.S, Toxicologist Jess Rowland 2/19/92
Section II, Toxicology Branch II (H7509C)

SECONDARY REVIEWER: K. Clark Swentzel K. Clark Swentzel 2/21/92
Head, Section II,Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 21-Day Dermal Toxicity **GUIDELINE:** 82-2

Caswell No. 315 K **MRID No. 419209-05** **HED PROJECT No. 1-2160**

TEST MATERIAL: Diethanolamine salt of 2,4-D.

REGISTRANT: PBI/Gordon Corporation, Kansas City, MO

TESTING LABORATORY: Springborn Laboratories,Inc., Spencerville, OH.

STUDY IDENTIFICATION: SLS Study No. 3229.1

TITLE OF REPORT: 21-Day Dermal Toxicity Study in Rabbits with Diethanolamine Salt of 2,4-D.

STUDY COMPLETION DATE: February 04, 1991 **AUTHOR:** J.C. Siglin

SUMMARY: Male and female rabbits received repeated dermal application of the Diethanolamine Salt of 2,4-Dichlorophenoxyacetic acid at doses of 0, 15, 148, or 443 mg/kg, 6 hours/day, 7 days/week for 21 days. Treatment had no adverse effect on survival, clinical signs, mean body weight, body weight gain, hematology, urinalysis or gross pathology. Food consumption at the high dose was decreased on several days during the first week of the study and was lower than controls on all other days. Signs of dermal irritation were observed in a dose-related manner with the severity ranging from mild at the low dose to severe at the high dose. Although minor dermal irritation was seen at the low dose, histopathology revealed no treatment-related lesions at this dose. At 148 and 443 mg/kg/day, 2,4-D DEA induced dermal lesions included increased incidence and/or severity of acanthosis, hyperkeratosis and chronic dermatitis. In addition, acute dermatitis, surface exudate, dermal hemorrhage and vesiculation of the epidermis were also seen at the high dose. 2,4-D DEA was also shown to be a hepatotoxin at a dose of 433 mg/kg/day, inducing liver lesions consisting of hypertrophy of hepatocytes and the presence of hyaline droplets within hepatocytes. These hepatic lesions correlated with the elevated serum enzyme levels [AST, ALT, and alkaline phosphatase] and increased absolute and relative liver weights in animals at the high dose. No liver lesions were seen in at 15 or 148 mg/kg/day groups.

The following NOEL's and LOEL's are established:

End Point	NOEL mg/kg/day	LOEL mg/kg/day	Basis for LOEL
Dermal toxicity	15	148	Microscopic dermal lesions
Systemic toxicity	148	443 [HDT]	Liver toxicity

VI. CORE CLASSIFICATION

Guideline; this study satisfies the requirements for a 21-day dermal toxicity study (82-3) in rabbits.

RANGE-FINDING STUDY

I. INTRODUCTION

A **range-finding study** was conducted with the Diethanolamine Salt of 2,4-D [2,4-D DEA] in rabbits to select dose levels for a full scale 21-day dermal toxicity study.

II. MATERIALS & METHODS

Test Material:	**2,4-D DEA** (lot No.0017; Purity: 73.09%).
Test Animals:	Male and female New Zealand White rabbits.
Dose Groups:	1 male and 1 female/dose level.
Dose Levels:	0, 15, 44, 148, 443, or 1476 mg/kg/day
Treatment:	Test material (clear,light brown liquid) in deionized water was applied topically on the dorsal shaved area (approximately 10% of the total body surface). The test site was covered with gauze/tape/wrap.
Exposure Time:	6 hours/day, 7 days/week for 21-days
Observations:	Mortality, moribundity, clinical signs, body weights (Days 1, 8, 15, and 22), and gross pathology.

III. RESULTS

Both rabbits treated at 1476 mg/kg/day died on study day 7. The male rabbit at 443 mg/kg/day was sacrificed on study day 6 due to a broken back. All other animals survived to termination. Clinical signs which preceded the animals that died [1476 mg/kg/day] included decreased activity, labored breathing, few feces, loss of fore and hind limb mobility, and wobbly gait. Treatment and dose-related dermal irritation was observed with the irritation being quite severe [leading to desquamation, thickening and/or eschar formation] at levels above 148 mg/kg/day. Dermal irritation at 15 mg/kg/day was limited to slight erythema. No treatment-related effects were observed in body weight gain or gross necropsy.

IV. CONCLUSION

Based on these findings, the dose levels selected for the full scale 21-day dermal toxicity study with **2,4-D DEA** were: 15, 148, and 443 mg/kg/day.

V. CORE CLASSIFICATION

Not applicable; range finding study to determine dose levels for a full scale study.

21-DAY DERMAL TOXICITY STUDY

I. INTRODUCTION

This Data Evaluation Report summarizes the experimental procedures and results of a 21-day dermal toxicity study in rabbits with 2,4-D DEA.

II. MATERIALS AND METHODS

1. Test Material

Chemical Name: Diethanolamine Salt of 2,4-D
Active Ingredient: 73.09%
Lot No.: 0017
Description: Clear, light brown liquid

2. Test Animals

Species: Rabbit
Strain: New Zealand White
Sex: Males and females
Age at Initiation: 22 weeks (M); 23 weeks (F)
Weight at Initiation: Males - 2.7 to 3.3 kg;
Females - 2.6 to 3.2 kg
Identification: Ear tags
Acclimation: 11 days
Health Status: Good
Housing: Individually in suspended wire mesh cages
Food: Certified Purina Rabbit Chow #5322 ad libitum
Water: Tap water ad libitum
Environment: Temperature - 67 ± 4°F; Humidity -40 to 60%
12 hr. light/dark cycle

3. Study Design

Group No.	No. of Animals Males	Females	Dose Level (mg/kg/day)[a]	Actual Test Material (mg/mL)
1 (vehicle control)	5	5	0	0
2 (Low-dose)	5	5	15	10.26
3 (Mid-dose)	5	5	148	101.25
4 (High-dose)	5	5	443	303.05

[a] Based on results of a 21-day pilot range-finding study.

4. **Test Material Formulation**

An appropriate amount of the test material for each group was weighed and sufficient amount of sterile distilled water was added to achieve the desired concentration. The concentration of each dosing solution was adjusted based on a test article activity of 73.09%. Dosing solutions were prepared fresh weekly and individual aliquots were stirred for approximately ten minutes prior to daily dispensation.

5. **Analyses of Dosing Solutions**

Concentration, homogeneity, and stability analyses of the dosing solution were performed prior to the initiation of the study.

6. **Treatment**

Approximately 24 hours prior to dosing, the fur was clipped dorsally and laterally from shoulder to rump to cover an area of approximately 10 % of the total body surface. Appropriate volume of the test material/vehicle mixture [dosing solution] was applied uniformly over the exposure area; the control group received distilled water. Each animal's dose was held in contact with the skin using a porous 8 ply 4" x 4" gauze dressing which secured in place using Blenderm tape. A stockinette sleeve was then place around the rabbit's torso and secured with athletic tape. To prevent possible ingestion of the test material, during the course of the 6 hour exposure period all animals wore flexible plastic restraint collars. At the end of the exposure period, the dressings and collars were removed and the treated area was wiped with clean gauze moistened with sterile water to remove any remaining test material. Rabbits were treated for 6 hours/day, 7 days/week for 21 days.

6. **Experimental Procedures**

Parameter	Time measured
Mortality and Moribundity	Twice daily
Dermal irritation	Daily prior to treatment
Body weight	Weekly
Food consumption	Daily
Hematology & Clinical Chemistry Urinalysis	Prior to initiation and at termination Termination

Hematology

Hematocrit	Leukocyte count (WBC)
Hemoglobin (HGB)	Platelet count
Erythrocyte count (RBC)	Leukocyte differential
Mean cell volume (MCV)	Mean cell hemoglobin concentration (MCHC)
Mean cell hemoglobin (MCH)	Reticulocyte count

Clinical Chemistry

Albumin	Globulin
Albumin/globulin (A/G) ratio	Alkaline Phosphatase
Blood Creatinine	Cholesterol
Triglycerides	Fasting Glucose
Aspartate aminotransferase (AST)	Alanine aminotransferase (ALT)
Total Bilirubin	Total Serum Protein
Sodium	Chloride
Potassium	Calcium
Blood urea nitrogen	

Urinalysis

Appearance	Bilirubin
Specific gravity	Occult blood
pH	Urobilinogen
Protein	Glucose
Ketone	Microscopic examination of sediment

7. Termination

At termination, animals were weighed, anesthetized with sodium pentobarbital, and sacrificed by exsanguination and were subjected to a complete necropsy. At necropsy the brain, kidneys, liver with drained gall bladder, thyroid, testes with epididymides and ovaries of all animals were weighed and organ-to-body weight ratios were calculated. Skin (treated and untreated), liver, kidneys, eyes, and target organs (those organs showing gross pathological changes) from all animals were fixed in 10% neutral-buffered formalin.

8. Histopathology

The tissues listed above from control and high-dose animals were trimmed and processed for histopathological evaluation.

9. Statistical Analyses

Statistical analyses were two-tailed with minimum significance level of 5%. One Way Analysis of Variance [ANOVA] was used for body weight, weight gain, food consumption and organ weight data. When significance was observed with ANOVA, control to treatment group comparisons were performed using Dunnett's Test.

10. Quality Assurance

The study was conducted and inspected in accordance with the Good Laboratory Practice Regulations, the Standard Operating Procedures of Springborn Laboratories, and the study Protocol. A quality assurance statement was signed and dated on February 4, 1991.

III. RESULTS

1. Analytical Data

Concentration analyses showed an average recovery of 99%, 97.9% and 98.% for nominal concentrations of 10.26, 101.25, and 303.05 mg/mL, respectively. The pretest stability analyses indicated the dosing solution to be stable [recovery range:100.1 to 103.0%] for up to 8 days in room temperature. Homogeneity analyses showed the dosing solution to be homogeneous.

2. Survival

All animals survived to terminal sacrifice on day 22.

3. Clinical Signs

No treatment-related clinical signs of toxicity were observed during the study.

4. Dermal Observations

No dermal irritation was observed in rabbits treated with distilled water [vehicle control]. However, dermal irritation was observed at all dose levels with the severity being dose-related. At 15 mg/kg/day, irritation was mild and consisted primarily of slight erythema. At 148 mg/kg/day, the irritation was more severe and was characterized by slight to moderate erythema, edema, and desquamation. At 443 mg/kg/day, the irritation progressed to eschar formation in most rabbits with additional observations of fissuring, thickening, and exfoliation. The dermal observations are summarized below:

MALES (Total Incidence/No.of Animals)			
Dermal Lesions from Day 1 - Day 22	Dose (mg/kg/day)		
	15	148	443
Erythema - Slight	50/5	21/5	36/5
Erythema - Moderate	2/1	76/5	36/5
Edema - Slight	2/1	75/5	20/5
Edema - Moderate	0	6/3	18/3
Desquamation - Slight	0	29/5	14/3
Desquamation - Moderate	0	25/3	10/2
Fissuring - Slight	0	0	32/3
Eschar - Partial	0	0	14/3
Eschar - Complete	0	0	27/3
Eschar - Exfoliation	0	0	27/3
Thickening of skin	0	3/1	4/3
Areas of eschar within patch site	0	0	4/2
Blanching	0	0	3/1

FEMALES (Total Incidence/No.of Animals)			
Dermal Lesions from Day 1 - Day 22	Dose (mg/kg/day)		
	15	148	443
Erythema - Slight	71/5	24/5	28/5
Erythema - Moderate	11/1	76/5	18/5
Edema - Slight	17/1	63/5	9/5
Edema - Moderated	0	15/4	5/4
Desquamation - Slight	0	14/4	0/0
Desquamation - Moderate	0	47/5	0/0
Fissuring - Slight	0	0	63/5
Eschar - Partial	0	0	2/1
Eschar - Complete	0	5/1	24/5
Eschar - Exfoliation	0	0	42/5
Thickening of skin	0	2/1	46/5
Areas of eschar within patch site	0	4/1	5/3
Blanching	0	2/1	16/5

5. **Body Weight**

Mean body weight an body weight gain were comparable between the treated and control groups. However, the cumulative weight for the 443 mg/kg/day males [91 ± 201.5 g] was appreciably lower than controls [268 ± 117.1 g].

6. **Food Consumption**

Males at 443 mg/kg/day consumed significantly [p <0.01] less food [g/animal/day and g/kg/day] on several days during the first week of the study and also on other days when compared to controls. No other statistically significant differences in food consumption were noted.

7. **Hematology, Clinical Chemistry, and Urinalysis**

No biologically significant changes were seen in mean hematology values in treated groups when compared to appropriate corresponding control group values. The sporadic statistically significant differences seen in a few hematology data were not considered to be treatment-related due to the low magnitude of the change, presence of similar differences at the pretreatment intervals, and/or lack of dose response.

Clinical chemistry data exhibited elevated serum enzyme levels in both sexes of rabbits at the high dose [443 mg/kg/day] on day 22 as shown below:

MALES

Parameter	0 mg/kg/day	443 mg/kg/day
AST [IU/L]	30.4 ± 8.1	32.8 ± 10.8
ALT [IU/L]	50.8 ± 14.2	113.2 ± 60.1*
ALK.PHOSPHATASE [IU/L]	93.2 ± 19.5	157.4 ± 68.7*

FEMALES

Parameter	0 mg/kg/day	443 mg/kg/day
AST [IU/L]	28.0 ± 6.9	92.4 ± 75.7*
ALT [IU/L]	41.6 ± 7.5	293.0 ± 289.8*
ALK.PHOSPHATASE [IU/L]	97.2 ± 42.5	449.4 ± 193.1*

* significantly different from controls at p <0.01 or 0.05

Urinalyses revealed a possible increase in the occurrence of occult blood in both sexes at 148 and 443 mg/kg/day. Microscopic analyses revealed a high urine RBC content in only one animal at 443 mg/kg/day. No other apparent differences in urinalysis data were noted.

8. **Gross Pathology**

No treatment-related gross pathological changes were seen. Sporadic findings of low incidence included pitted and small kidneys, enlarged lymph nodes, mottled lungs, yellow-tan focus on the liver, reddened thyroid, and mass in the abdominal cavity.

9. **Organ Weight**

The mean absolute and relative liver weight values were increased in a dose-related manner with the difference reaching statistical significance [$p < 0.01$] at 148 and 443 mg/kg/day. Other organ weight data were comparable between the treated and control groups.

10. **Histopathology**

Histopathology revealed no treatment-related microscopic changes in the treated skin of rabbits at 15 mg/kg/day. Treatment-related dermal lesions observed at 148 and 443 mg/kg/day levels consisted of an increased incidence and/or severity of acanthosis, hyperkeratosis and chronic dermatitis. Acute dermatitis, surface exudate, dermal hemorrhage and vesiculation of the epidermis were also seen in rabbits at the high dose. Skin lesions are summarized below:

No. of Animals with Lesions	Dose [mg/kg/day]							
	0		15		148		443	
Treated Skin	♂	♀	♂	♀	♂	♀	♂	♀
Acanthosis	2	0	0	1	5	4	4	5
Dermatitis, acute	0	0	0	0	0	0	1	0
Dermatitis, chronic	2	1	1	1	1	4	1	4
Exudate, epidermal surface	0	0	0	0	0	0	1	2
Hemorrhage	0	0	0	0	0	0	2	2
Hyperkeratosis	0	0	0	0	5	5	5	5
Necrosis, mild	0	0	0	1	0	0	0	0
Vesiculation, mild	0	0	0	0	0	0	0	1

Treatment-related liver lesions limited to the high dose were characterized by hepatocyte hypertrophy [5 ♂ and 5 ♀] and the presence of homogenous, faintly eosinophilic hyaline droplets within hepatocyte cytoplasm [2 ♂ and 5 ♀]. No treatment-related liver lesions were seen at 15 or 148 mg/kg/day. Other microscopic changes were typical of common spontaneous lesions in rabbits of this age.

IV. DISCUSSION

Male and female rabbits received repeated dermal applications of the Diethanolamine Salt of 2,4-Dichlorophenoxyacetic acid at doses of 0, 15, 148, or 443 mg/kg, 6 hours/day, 7 days/week for 21 days. Treatment had no adverse effect on survival, clinical signs, mean body weight, body weight gain, hematology, urinalysis or gross pathology. Food consumption at the high dose was decreased on several days during the first week of the study and was lower than controls on all other days. Signs of dermal irritation were observed in a dose-related manner with the severity ranging from mild at the low dose [15 mg/kg/day] to severe at the high dose. Although minor dermal irritation was seen at the low dose,histopathology revealed no treatment-related lesions at this dose. At 148 and 443 mg/kg/day, 2,4-D DEA induced dermal lesions included increased incidence and/or severity of acanthosis, hyperkeratosis and chronic dermatitis. In addition, acute dermatitis, surface exudate, dermal hemorrhage and vesiculation of the epidermis were also seen at the high dose. 2,4-D DEA was also shown to be a hepatotoxin at a dose of 433 mg/kg/day, inducing liver lesions consisting of hypertrophy of hepatocytes and the presence of hyaline droplets within hepatocytes. These hepatic lesions correlated with the elevated serum enzyme levels [AST, ALT, and alkaline phosphatase] and increased absolute and relative liver weights in animals at the high dose. No liver lesions were seen in at 15 or 148 mg/kg/day groups.

V. CONCLUSION

Based on the results of this study, the following NOEL's and LOEL's are established:

End Point	NOEL mg/kg/day	LOEL mg/kg/day	Basis for LOEL
Dermal toxicity	15	148	Microscopic dermal lesions
Systemic toxicity	148	443 [HDT]	Liver toxicity

VI. CORE CLASSIFICATION

Guideline; this study satisfies the requirements for a 21-day dermal toxicity study (82-3) in rabbits.

END